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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,883	09/19/2003	Chong-Sheng Yuan	466992001100	6779

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MORRISON & FOERSTER LLP
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EXAMINER

HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
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1652

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06/23/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/665,883	Applicant(s) YUAN, CHONG-SHENG	
	Examiner Richard G. Hutson	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 February 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 12, 21-23, 31-34, 37-42, 44-48, 50-55, 58-65 and 67-72 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 23 is/are allowed.
- 6) ☒ Claim(s) 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65 and 67-72 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's amendment of claims 1, 23, 31, 39, 45, 50, 60, 68, in the paper of 2/24/2009, is acknowledged. Claims 1, 12, 21-23, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72 are still at issue and are present for examination.

Applicants' arguments filed on 2/24/2009, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection was stated in the previous office action as it applied to previous claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72. In response to the

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rejection, applicants have amended claims 1, 23, 31, 39, 45, 50, 60, 68 and traverse the rejection as it applies to the newly amended claims.

Applicants traverse this rejection on a number of different bases. First, applicants traverse on the basis that in view of the comments relating to the allowability of claim 23, Applicants do not see how the Office can object to the portions of the claim reciting "a first peptidyl fragment comprising a bacterial leader sequence comprising an amino acid sequence as set forth in SEQ ID NO: 1," a second peptidyl fragment comprising the amino acid sequence as set forth in SEQ ID NO:2," and "a third peptidyl fragment comprising an amino acid sequence as set forth in SEQ ID NO:3."

Applicants further assert that conservative amino acid substitutions of amino acid sequences were well-known in the art, and were fully described in the specification at paragraph [0018] and that a person of ordinary skill in the art could empirically replace an amino acid in SEQ ID NO:2 with a conservative amino acid substitution, and test the resultant peptide to determine whether it has retained the requisite 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2. Applicants submit that this type of testing is further described in the specification, for example at paragraph [0043].

Applicants submit that a person of skill in the art, reading the specification, would be able to design and test the derivative peptides for the requisite activity.

Furthermore, applicants submit that the art discloses sufficient relevant identifying characteristics such that a person of skill would be able to correlate the

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structure of SEQ ID NO:2 with the requisite functional activity as described in detail in Example 11B of the written description guidelines.

Applicants submit that SEQ ID NO:2 is the Hal2p protein and applicants submit that this protein was known in the art at the time the application was filed, as evidenced by paragraph [0040]. and for example, Albert et al. (*X-ray Structure of Yeast Hal2p, a Major Target of Lithium and Sodium toxicity, and Identification of Framework Interactions Determining Cation Sensitivity*, J. Mol. Biol. (2000) 295:927-938, Exhibit A) who teach the crystal structure of Hal2p complexed with magnesium, lithium AMP and Pi. Hal2p is a two-domain structure linked at residue 220, containing an N-terminal domain, and a C-terminal domain (*id.*, at page 928, right column).

Applicants submit that a skilled artisan at the time of the invention would have understood that high conservation of amino acid sequences typically has important functional implications, and therefore highly conserved amino acids within the family should not be mutated if one desires to retain biological function, or alternatively, biological function is more likely to be retained if conservative substitutions are made in these regions. Clearly, a large of amount of structure-function correlation data had been published at the time the application had been filed.

In light of the foregoing discussion, Applicants respectfully submit that the specification, combined with the knowledge in the art at the time of the present invention, provides sufficient disclosure to convey to a person skilled in the art that Applicants were in possession of the claimed invention. Accordingly, Applicants

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respectfully submit that this written description rejection under 35 U.S.C. § 112, first paragraph may properly be withdrawn.

Applicant's amendment and complete argument is acknowledged and has been carefully considered, however is found nonpersuasive on the following basis.

Applicants initial comments regarding the allowability of claim 23, and the Office's objection to the portions of the claim reciting "a first peptidyl fragment comprising a bacterial leader sequence comprising an amino acid sequence as set forth in SEQ ID NO: 1," a second peptidyl fragment comprising the amino acid sequence as set forth in SEQ ID NO:2," and "a third peptidyl fragment comprising an amino acid sequence as set forth in SEQ ID NO:3.", are not entirely clear, however, it is pointed out to applicants that the breadth of applicants claims is the result of such language. Thus applicants reference to "an amino acid sequence as set forth in SEQ ID NO:1" or SEQ ID NO:3 for that matter, continues to be interpreted by the office as the amino acid sequence of SEQ ID NO:1, as well as any amino acid sequence fragment of SEQ ID NO:1. This interpretation of the breadth of applicant's claims certainly is related to whether applicants have adequately described the claims.

Applicants traversal regarding conservative amino acid substitutions of amino acid sequences being well-known in the art, and fully described in the specification at paragraph [0018] and that a person of ordinary skill in the art could empirically replace an amino acid in SEQ ID NO:2 with a conservative amino acid substitution, and test the resultant peptide to determine whether it has retained the requisite 50% of the 3'(2'),5'-

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bisphosphonate activity of SEQ ID NO:2 is acknowledged and appreciated, however, this argument is not persuasive in overcoming the current rejections on the basis that it remains that applicants claims are not limited to merely those derivatives consisting of conservative amino acid substitutions. While it is acknowledged that applicants referred to derivatives certainly encompass conservative substitutions, the claims are not interpreted as being limited to such with regard to the breadth of the encompassed derivatives. Those derivatives that are not encompassed by the mere conservative amino acid substitutions remain inadequately described. This in combination with interpreted breadth of the claims that are not limited structurally with regard to SEQ ID NO:2, by virtue of "derivative thereof", lead to a lack of adequate written description. While a person of skill in the art, reading the specification, would be able to design and test the many of the derivative peptides for the requisite activity, applicants are reminded that the current rejection is based upon a lack of written description and not a lack of enablement and the currently claimed genus remains inadequately described.

Thus, applicants submission that the art discloses sufficient relevant identifying characteristics such that a person of skill would be able to correlate the structure of SEQ ID NO:2 with the requisite functional activity as described in detail in Example 11B of the written description guidelines, is not found persuasive in the description of the currently claimed genus, which contrary to Example 11B of the written description guidelines does not place structural limitations relevant to SEQ ID NO:2 on the breadth of the claims .

Given this lack of representative species, beyond those drawn to conservative substitutions of SEQ ID NO:2, as encompassed by the full breadth of the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65 and 67-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric protein having nucleotidase activity comprising the amino acid sequence of SEQ ID NO: 4, does not reasonably provide enablement for any chimeric protein having the enzymatic activity of a nucleotidase, comprising any peptidyl fragment comprising a bacterial leader sequence comprising an amino acid sequence set forth in SEQ ID NO: 1, any peptidyl fragment comprising a derivative of SEQ ID NO:2 having a conservative amino acid substitution wherein the derivative retains at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2 and a peptidyl fragment comprising an amino acid sequence having as set forth in SEQ ID NO: 3 and methods of methods of their use, encompassed by these claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection was stated in the previous office action as it applied to previous claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72. In response to the rejection, applicants have amended claims 1, 23, 31, 39, 45, 50, 60, 68 and traverse the rejection as it applies to the newly amended claims.

Applicants traverse this rejection as above on a number different basis.

Applicants note that the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention and that while compliance with 35 U.S.C. § 112, first paragraph enablement does not require that specific portions of any amino acid sequence be identified, it should not require undue experimentation to determine those portions of the sequence that are capable of mediating a biological function similar to that mediated by the protein of SEQ ID NO:2.

Applicants submit that as discussed previously and above, the art of preparing a polypeptide with a conservative amino acid mutation compared to another polypeptide having a fully defined sequence and a certain type of known biological activity was well-settled and routine at the time the present application was filed.

Applicant's amendment and applicants complete argument is acknowledged and has been carefully considered, however, is not found persuasive for the reasons previously made of record and repeated herein. As discussed above, the breadth of applicants claims are not limited merely to those chimeric proteins comprising the amino acid sequences of SEQ ID NO:1, SEQ ID NO:3 and SEQ ID NO:2 or derivatives of SEQ ID NO: 2 having only conservative amino acid substitutions of SEQ ID NO: 2, but rather

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the claims are limited to those chimeric proteins comprising derivatives of SEQ ID NO: 2 which retain 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2.

While those chimeric proteins comprising conservative substitutions of SEQ ID NO:2 may be enabled, those proteins encompassed by derivatives of SEQ ID NO:2, which have no structural limitations relative to SEQ ID NO:2 are not.

While methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants useful as nucleotidases requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. For the rejected claims with no structural limitations, would clearly constitute **undue** experimentation. Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would allow for finding a few active mutants within several hundred thousand or up to about a million inactive mutants as is the case for the claims limited to 95% identity (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish) but finding a few mutants within several billion or more as in the claims to 90% or less identity would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required by the breadth of the current claims, the specification must provide a reasonable amount of guidance with respect to the direction in which the

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experimentation should proceed. Such guidance has **not** been provided in the instant specification.

Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the 3'(2'),5'-bisphosphate nucleotidase activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable, it would require undue experimentation for one skilled in the art to arrive at the majority of those chimeric proteins having the enzymatic activity of a nucleotidase, comprising any peptidyl fragment comprising a bacterial leader sequence comprising an amino acid sequence set forth in SEQ ID NO: 1, any peptidyl fragment comprising a derivative of SEQ ID NO:2 having a conservative amino acid substitution wherein the derivative retains at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2 and a peptidyl fragment comprising an amino acid sequence having as set forth in SEQ ID NO: 3.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any chimeric protein having the enzymatic activity of a nucleotidase, comprising any derivative of SEQ ID NO:2 having a conservative amino acid substitution wherein the derivative retains at least 50% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2 and methods of their use. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of

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polypeptides and methods having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rg
6/19/2009

/Richard G Hutson/
Primary Examiner, Art Unit 1652